AFRRI SR73-15
SEPTEMBER 1973

AFRRI
SCIENTIFIC
REPORT

# BONE MARROW RESPONSE OF BEAGLES TO FRACTIONATED DOSES OF MIXED GAMMA-NEUTRON RADIATION

J. E. West
F. A. Mitchell
S. R. Jones
J. Witz

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland



AFRRI SR73-15

Research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences - National Research Council.

AFRRI SR73-15
September 1973

# BONE MARROW RESPONSE OF BEAGLES TO FRACTIONATED DOSES OF MIXED GAMMA-NEUTRON RADIATION

J. E. WEST
F. A. MITCHELL
S. R. JONES
J. WITZ

Joe E. West

JOE E. WEST
Lieutenant Colonel, USAF, VC
Chairman
Radiation Biology Department

Myron I. Varon

MYRON I. VARON
Captain MC USN
Director

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

---

ACKNOWLEDGMENT

The authors are grateful to S. G. Levin and A. S. Evans for assistance with computer data handling procedures; to J. P. Vagher and D. F. Trainor for technical assistance with bone marrow aspirations and clinical laboratory and necropsy procedures; to G. D. Lee for preparing histologic sections; to D. M. Verrelli, C. Carter and J. T. Istock for dosimetry support; to the entire staffs of the Reactor Division and the Laboratory Animal Support Services; and to N. K. Plitt and C. H. Poppe for stenographic and manuscript preparation support.

TABLE OF CONTENTS

## LIST OF FIGURES



## LIST OF TABLES

## FOREWORD
(Nontechnical summary)

The objective of this study was to determine the relative lethality following median lethal doses of mixed gamma-neutron radiations in beagles given either as single brief exposures or as four fractions consecutively administered at 24-hour intervals. Since the response of bone marrow cell systems in large animals after median lethal doses has been limited mainly to qualitative descriptions, quantitative changes were determined from rib marrow aspirates obtained at regular intervals during the 1 month period of study. Selected peripheral blood cell and clinical indices were also examined.

Results of this study showed that fractionated exposures did not result in greater lethality as previously hypothesized. On the contrary, single irradiations were more lethal. The difference in lethality was first evident at 225 rads and became larger with increasing dose. There were two deaths in six animals fractionally irradiated at 215 rads, the only mortality shown in fractionated dosage groups.

The postirradiation response of marrow cell systems was characterized by an early phase of cellular depopulation due to disappearance of immature stages within the dividing and maturing compartment, followed by a brief nadir which occurred at a time somewhat independent of dose or mode of exposure. Subsequently, the regenerative phase seen only in survivors restored marrow cellularity to near base-line values by the end of the study.

The time to reach the nadir and the eventual minimum levels attained by dividing and maturing marrow granulocyte precursor cells were similar after single and fractionated doses. An inverse dose effect relationship occurred between the final recovery

level achieved by immature marrow granulocytes and total dose after fractionated and single irradiations. Survivors of fractionated irradiation showed a lesser capacity to restore neutrophils to the circulation than survivors of comparable doses given as single exposures.

The time at which postirradiation minima were reached by platelets and the degree of platelet depression were usually independent of both total dose and mode of irradiation. The greatest level of recovery of circulating platelets was achieved in animals fractionally irradiated with 225 rads and 240 rads.

The pattern of lethality response as well as measurements of bone marrow cell indices yielded no information which would suggest that increased marrow cell death occurred following fractionated exposures, as would have been expected if mitotic cell cycle synchronization was induced by the carefully spaced dose fractions.

ABSTRACT

Male beagles were bilaterally exposed to mixed gamma-neutron radiation from the AFRRI-TRIGA reactor. The dose rate was 20 rads/minute for all irradiations and midline tissue doses were 215 rads, 225 rads and 240 rads. At each dose approximately one-half of the animals received a single irradiation while the others were given one-fourth the dose each day for 4 consecutive days. The objective of this study was to determine if doses in the median lethal range delivered in four equal fractions at 24-hour intervals were more lethal and more damaging to survival-limiting hematopoietic cell renewal systems than similar, unfractionated doses. Serial rib marrow aspirates and peripheral blood samples were studied for 32 days after irradiation. Single irradiations were the more lethal, first evident at 225 rads and increasing markedly in effectiveness at 240 rads. Radiation-induced changes in bone marrow cellularity were similar after single and fractionated irradiations. Thus, data did not support an enhanced effect on key end points as would have been expected from mitotic cell cycle synchronization and increased marrow cell death from the carefully spaced dose fractions.

# I. INTRODUCTION

Most of the current knowledge of the biological effects of ionizing radiation on mammalian systems has been derived from acute, single midlethal exposures. The possibility of multiple exposures must also be addressed when considering operations in hostile nuclear environments, in peacetime nuclear accidents, and in clinical radiotherapy.

Little is known regarding the effects of dose fractionation of conventional low linear energy transfer (LET) radiation on the hematopoietic system of man.[9] Considerably less information is available on this system's response to fractionated doses of particulate radiation in the $LD_{50}$ dosage range.[9] Dose fractionation of low LET radiation strongly influences early postirradiation responses and increases the total dose required to produce lethality from the bone marrow syndrome.[9] Under conditions involving specific dose fractionation schedules and rapidly dividing cell renewal systems such as bone marrow and seminiferous epithelium, an increased dose response has been reported for 60-day lethality and sterility in dogs.[4,10] The unexpected increased mortality response was seen when a single dose of 300 R (midline air dose) x radiation was given whole-body as four equal fractions 24 hours apart.[10] The 24-hour time interval between fractions appeared to be critical to the increased effect since results from administering the fractions at 12- and 48-hour intervals were as expected from acute and protracted exposures, respectively. Thus, it is essential to assess the relative effectiveness of fractionated versus single exposures of mixed gamma-neutron radiation on selected radiobiological end points in an animal model, the hematopoietic system of which is comparable to that of man.

The purpose of this study was to determine the comparative lethality response and damaging effects on bone marrow cell systems in beagles after midlethal doses of mixed gamma-neutron radiations given either as single, brief exposures or as four equal dose fractions 24 hours apart. The early postirradiation lethality response was of primary interest. Additionally, because of the lack of information on quantitative changes which occur in bone marrow cellularity of larger animals after median lethal doses,[2] specific indices of marrow cell kinetics were also determined.

## II. MATERIALS AND METHODS

Laboratory animals. The adult male beagles used in this study and their related care and husbandry have been previously described.[15] Each experimental group consisted of approximately eight beagles, six for irradiation and two for nonirradiated controls, assigned by using a table of random numbers. Except for irradiation, animals within each group were handled identically. Data from controls were used to prevent responses to environmental factors from being attributed to radiation. All animals had been previously immunized against common canine diseases, dewormed when appropriate, and properly conditioned upon arriving at the AFRRI from the boarding facility.*

Animal irradiations. The AFRRI-TRIGA reactor and its exposure facilities, as previously described,[6] were used for all irradiations. Beagles were bilaterally irradiated in the reactor's mixed gamma-neutron field at approximately 20 rads/minute. Each experimental group received a midline tissue dose (MTD) of 215, 225 or 240 rads, either as a single or a fractionated exposure, the latter given in four equal fractions 24 hours apart. Depth-dose measurements indicated that all irradiations were Class A

* Hazleton Research Farms, Inc., Cumberland, Virginia; ANTEC Corporation, Leesburg, Virginia

uniform as defined in ICRU Report 10e.[7] Stress due to mechanical factors related to the irradiation procedure was kept to a minimum by conditioning each dog to its adjustable Lucite exposure container during the week preceding irradiation. After irradiation each dog was observed daily and was physically examined at the time of bone marrow and peripheral blood sampling.

Experimental procedures.

Bone marrow aspirations. Bone marrow samples were generally obtained three times per week postirradiation, consistently at the same time of day. Marrow was also sampled after each dose fraction from dogs irradiated on the fractionation schedule. The techniques used to obtain rib bone marrow aspirates under local anesthesia and the related methods for quantitating bone marrow cellularity have been previously reported.[14,15] Values for total nucleated marrow cells/$mm^3$, differential marrow cell counts, and the related absolute number of nucleated marrow cells from the right and left ribs were averaged at each sampling for each dog. A minimum of 500 nucleated marrow cells were differentiated on two Wright's-Leishman-stained cover slip smears from each sample and the myeloid: erythroid (M:E) ratio calculated. Absolute numbers of each marrow cell type per cubic millimeter of marrow were obtained by multiplying the total nucleated cell count/$mm^3$ by the appropriate differential percentage after correcting for hemodilution as previously described.[15] Data derived from 216 bone marrow aspirates from the right and left 8th through 11th ribs in 27 adult male beagles served as the preirradiation base line against which postirradiation changes in marrow cellularity were compared.

Hematology. Peripheral blood for complete blood counts (CBC) was obtained aseptically by venipuncture from the external jugular vein prior to daily feeding three times each week postirradiation. Standard methods were employed during all hematological determinations.[12,16]

Pathology. Necropsies were performed on all animals. Evaluation of pathologic changes in hematopoietic tissues was emphasized.

Data handling. Data processing of the extensive numerical values from bone marrow and peripheral blood was accomplished with the aid of the AFRRI Scientific Data Systems (SDS) 920 computer.

## III. RESULTS

Mortality responses. Two of the six dogs fractionally irradiated at 215 rads died, the only mortality produced by fractionated exposures. Single brief irradiations were the most lethal. Two of the four dogs irradiated at 225 rads died while five of six dogs died after the 240-rad exposure (Table II).

Bone marrow cell responses. The changes which occurred in bone marrow cell differentials and in total nucleated marrow cells/$mm^3$ after single and fractionated doses of 215 rads, 225 rads and 240 rads are shown in Figures 1, 2 and 3, respectively.

Reduction in total nucleated marrow cells/$mm^3$ was evident within 24 hours after single exposures and at the time of completing the fractionated exposures, more prominent after the two highest exposures. Beginning regeneration toward preirradiation numbers was evident in survivors after 3 weeks.

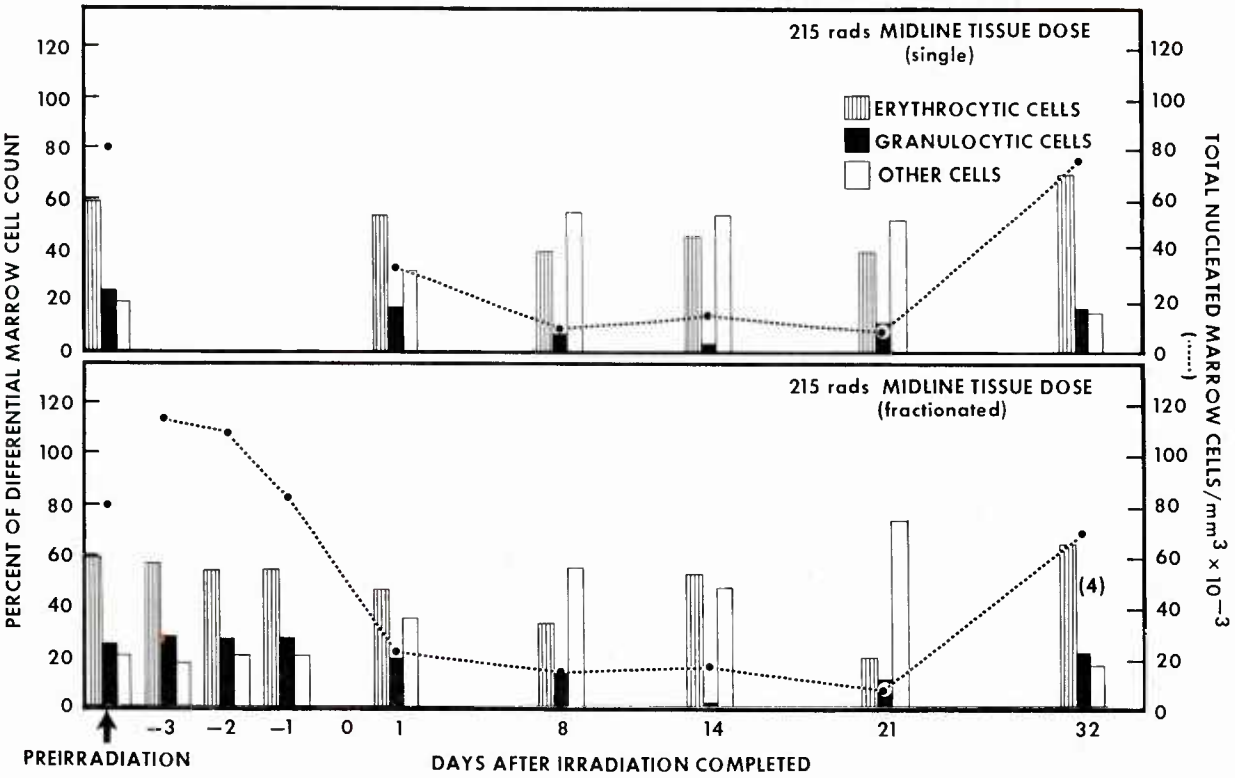


Figure 1. Response of bone marrow differential and total nucleated cell values after single and fractionated irradiation at 215 rads in six beagles. Only four animals survived the fractionated dose.

The most marked change in marrow differential cell values occurred after the 240-rad exposure. Relative percentage increases in radioresistant cell types (other cells) occurred during the period of maximum depression in total nucleated marrow cells/$mm^3$, most marked after the 240-rad single exposure. Granulocytic series cells normally comprised less than 5 percent of the myelogram by 14 days after irradiation. Regeneration of marrow cellularity by 3 weeks in survivors was accompanied by a normalization of percentages of bone marrow cell compartments.

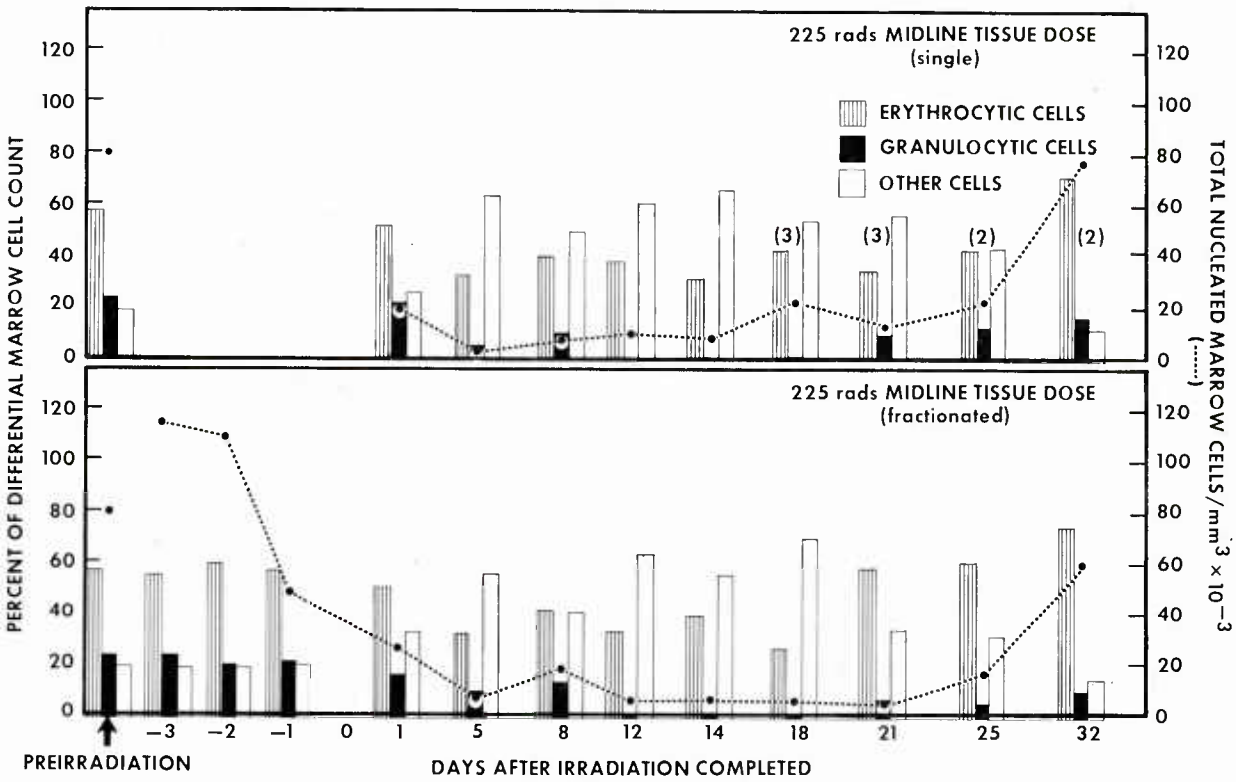


Figure 2. Response of bone marrow differential and total nucleated cell values after single and fractionated irradiation at 225 rads. Four animals were used in the single dose and two survived. Six animals were used in the fractionated dose with all surviving.

Key responses shown by survival-dependent hematopoietic cell lines, e.g., granulocytic and thrombocytic, after single and fractionated exposures are described in Tables I through IV.

With minor exceptions, the time of occurrence of the nadir and the extent of maximum depression during the degenerative phase of dividing and maturing (D & M) granulocytic cells were generally independent of total dose and mode of irradiation (Table I).

The onset of recovery for both the immature marrow granulocytes and the mature circulating neutrophils ranged between 2 and 3 weeks (Table II). The delayed regenerative onset in animals irradiated with a fractionated dose of 225 rads was an exception.

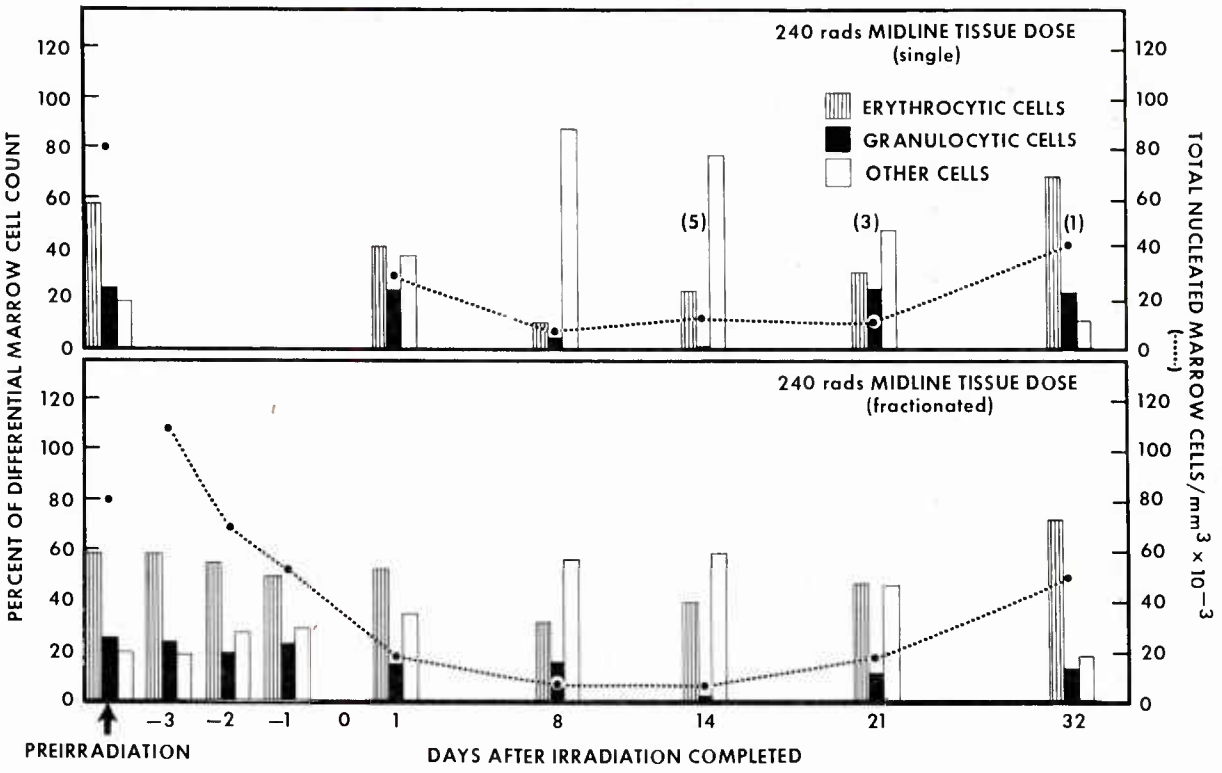


Figure 3. Response of bone marrow differential and total nucleated cell values after single and fractionated irradiation at 240 rads in six beagles. One animal survived the single dose.

An inverse dose-effect relationship existed between the recovery level achieved by immature marrow granulocytes and total dose after both fractionated and single irradiations. Survivors of fractionated irradiation showed a lesser capacity to restore neutrophils to the circulation than survivors of comparable doses given as single exposures. The D & M granulocyte precursors also showed this pattern following exposures at 215 and 225 rads.

The time at which postirradiation platelet minima were reached was generally independent of both total dose and mode of irradiation, e.g., single or fractionated,

Table I. Response of Granulocytic Cell Renewal System: Degenerative Phase

| Midline tissue dose (rads) | Compartment | Time to minimum (days) | | Percent preirradiation level at nadir | |
|---|---|---|---|---|---|
| | | Single | Fractionated | Single | Fractionated |
| 215 | Marrow (D & M)* | 14 | 14 | 0.2 | 0.5 |
| | Blood (Neutrophils) | 18 | 18 | 7 | 4 |
| 225 | Marrow (D & M) | 12 | 12 | 0.0 | 0.1 |
| | Blood (Neutrophils) | 18 | 21 | 4 | 7 |
| 240 | Marrow (D & M) | 14 | 14 | 0.6 | 0.2 |
| | Blood (Neutrophils) | 14 | 18 | 1 | 4 |

* Dividing and maturing cells (myeloblasts, progranulocytes, myelocytes)

Table II. Response of Granulocytic Cell Renewal System: Regenerative Phase and Lethality

| Midline tissue dose (rads) | Compartment | Time of beginning recovery (days) | | Terminal percent of preirradiation level | | Fraction of animals surviving | |
|---|---|---|---|---|---|---|---|
| | | Single | Fractionated | Single | Fractionated | Single | Fractionated |
| 215 | Marrow (D & M)* | 21 | 21 | 74 | 43 | 6/6 | 4/6 |
| | Blood (Neutrophils) | 21 | 21 | 95 | 59 | | |
| 225 | Marrow (D & M) | 14 | 14 | 48 | 25 | 2/4 | 6/6 |
| | Blood (Neutrophils) | 21 | 25 | 63 | 62 | | |
| 240 | Marrow (D & M) | 21 | 21 | 17 | 18 | 1/6 | 6/6 |
| | Blood (Neutrophils) | 18 | 21 | 139 | 59 | | |

* Dividing and maturing cells (myeloblasts, progranulocytes, myelocytes)

and ranged between 14 and 21 days (Table III). The nadir reflected marked thrombocytopenic levels in all groups and appeared to be independent of both total dose and irradiation method. Circulating platelets were absent at the nadir in animals which received the single 240-rad irradiation.

Platelet regeneration occurred promptly after the nadir (Table IV). The time of onset was directly influenced by the time at which the nadir was reached, e.g., the earlier the nadir the earlier the onset of platelet regeneration. Animals which received 225 rads by dose fractionation showed the most delayed and the severest platelet minimum. However, these animals regenerated approximately two-thirds of their

Table III. Response of Thrombocytic Cell Renewal System: Degenerative Phase, Circulating Platelets

| Midline tissue dose (rads) | Time to minimum (days) | | Percent preirradiation level at nadir | |
|---|---|---|---|---|
| | Single | Fractionated | Single | Fractionated |
| 215 | 18 | 18 | 0.9 | 1.4 |
| 225 | 14 | 21 | 2.5 | 0.4 |
| 240 | 18 | 18 | 0.0 | 1.0 |

Table IV. Response of Thrombocytic Cell Renewal System: Regenerative Phase, Circulating Platelets

| Midline tissue dose (rads) | Time of beginning recovery (days) | | Terminal percent of preirradiation level | | Fraction of animals surviving | |
|---|---|---|---|---|---|---|
| | Single | Fractionated | Single | Fractionated | Single | Fractionated |
| 215 | 21 | 21 | 31 | 39 | 6/6 | 4/6 |
| 225 | 18 | 25 | 28 | 63 | 2/4 | 6/6 |
| 240 | 21 | 21 | 68 | 53 | 1/6 | 6/6 |

preirradiation platelet levels by 32 days, compared to the approximately 40 percent and 50 percent levels achieved by the 215-rad and 240-rad fractionally irradiated groups, respectively. The survivor from the single 240-rad exposure showed intense thrombocytopoiesis terminally.

Grossly detectable hemorrhagic signs, first evident in the form of petechial to ecchymotic foci on penile mucosa, subsequently as subcutaneous hemorrhage at sites of venipunctures and bone marrow aspirations, coincided with thrombocytopenia and prolonged blood coagulation time. The disappearance of hemorrhagic lesions coincided with a return of circulating platelets and blood coagulation times toward preirradiation levels in survivors.

Moderate to marked hemorrhage within organs, body cavities, and subcutaneously characterized gross pathologic change in nonsurvivors. Bone marrow was dark red and mushy. Lymph nodes were enlarged to approximately two to five times normal size due to hemorrhage and edema. Spleen and lymph nodes showed a marked reduction of lymphoid follicles. Pathologic findings were not unique from those extensively reported for the hematopoietic syndrome.

## IV. DISCUSSION

The 100 percent survival of animals fractionally irradiated at 225 rads or 240 rads compared to mortalities of 50 percent and 83 percent, respectively, after comparable doses administered singly, does not support the hypothesis that fractionation of irradiation results in a greater damaging effect on survival-limiting marrow cell systems than single exposures. An unexplained exception was the 33 percent lethality

following the 215-rad fractionated dose compared to the 100 percent survival of animals receiving this dose as a single exposure.

The postirradiation response shown by marrow cell systems in all irradiated dogs was characterized by an early phase of marked cellular depopulation and an associated decline in numbers of mature circulating cells. Following a brief nadir which appeared to occur at a time somewhat independent of dose or mode of irradiation, e.g., single or fractionated, marrow cell regeneration began in survivors. The abortive increase in cell numbers seen during the regenerative phase of marrow recovery in beagles following single sublethal exposures to $^{60}$Co gamma radiation[14] was not evident.

The mechanism of radiation-induced marrow injury is attributed mainly to death of the radiosensitive stem cells and differentiating and dividing cells and to damage to the marrow microenvironment, particularly the sinusoidal microcirculation.[3,11] Progressive maturation depletion of the surviving insensitive nondividing stages contributes to the progressive decline of nucleated marrow cells during the degenerative phase. Marrow cell regeneration is due to stem cells which not only survive the radiation insult, but which also have the proliferative capacity to repopulate the marrow stem cell pool and produce hematopoietic cells which mature into functional cells for the circulation.[1] That marrow cell regeneration after irradiation injury accompanies a concomitant return of a normal appearing sinusoidal pattern was demonstrated by Knospe et al.[8]

The array of variables which influence the response of dose fractionation or protraction, i.e. total dose, number of fractions, interval between fractions, has been

described.[9] The net biological effect of a given total dose is usually reduced by fractionation.[9] However, critical dose-time relationships exist in connection with the effects of fractionated irradiation on cell renewal systems.[4] Radiation-induced synchrony of the mitotic cell cycle resulting in the synchronously progressing cohort of cells being made more sensitive to subsequent dose fractions was the probable mechanism of action of the increased effects reported for 60-day lethality[10] and sterility[4] in beagles after fractionated exposures.

The phenomenon of cyclic radiosensitivity has been demonstrated in both DNA synthesis of bone marrow stem cells as well as in acute lethal sensitivity of mice after sublethal conditioning doses of x irradiation.[5, 13] A synchronous repopulation of stem cells surviving the conditioning dose was the explanation given.

The findings of this investigation suggest that the individual dosage fractions were of insufficient size to synchronize the mitotic cell cycle of the rapidly dividing marrow cell renewal systems to create a more sensitive cell population. The lesser lethality response from fractionated irradiations suggested that dividing the dose into four equal fractions, each separated by a 24-hour interval, permitted sufficient repair to occur over the 4-day period of irradiation to reduce the net damaging effect compared to that from similar doses given as single brief exposures.

## REFERENCES


1. Bond, V. P. Radiobiological bases for the understanding of the hematological consequences of radiation exposure. In: Manual on Radiation Haematology, Chapter 4, pp. 71-78. Vienna, International Atomic Energy Agency, Technical Report Series No. 123, 1971.

2. Bond, V. P., Fliedner, T. M. and Archambeau, J. O. Mammalian Radiation Lethality, A Disturbance in Cellular Kinetics, pp. 159-230. New York, N. Y., Academic Press, 1965.

3. Bond, V. P., Fliedner, T. M. and Usenik, E. Early bone marrow hemorrhage in the irradiated dog. Arch. Pathol. 73:13-29, 1962.

4. Casarett, G. W. and Eddy, H. A. Fractionation of dose in radiation-induced male sterility. In: Dose Rate in Mammalian Radiation Biology, Proceedings of a Symposium co-sponsored by UT-AEC Agricultural Research Laboratory, Brown, D. G., Cragle, R. G. and Noonan, T. R., editors, pp. 14.1 - 14.10. Oak Ridge, Tennessee, United States Atomic Energy Commission, Division of Technical Information, CONF-680410 (TID-4500), 1968.

5. Frindel, E., Charruyer, F., Tubiana, M., Kaplan, H. S. and Alpen, E. L. Radiation effects on DNA synthesis and cell division in the bone-marrow of the mouse. Int. J. Radiation Biol. 11:435-443, 1966.

6. George, R. E., Stanley, R. E., Wise, D. and Barron, E. L. The acute mortality response of beagles to mixed gamma-neutron radiations and 250 kVp x rays. Bethesda, Maryland, Armed Forces Radiobiology Research Institute Scientific Report SR68-3, 1968.

7. International Commission on Radiological Units and Measurements (ICRU) Report 10e, 1962. Radiobiological dosimetry. National Bureau of Standards Handbook No. 88. Washington, D. C., U. S. Government Printing Office, 1963.

8. Knospe, W. H., Blom, J. and Crosby, W. H. Regeneration of locally irradiated bone marrow. I. Dose dependent, long-term changes in the rat, with particular emphasis upon vascular and stromal reaction. Blood 28:398-415, 1966.

9. Langham, W. H., editor. Radiobiological Factors in Manned Space Flight. Chapter 3. Factors modifying radiation response, pp. 27-48. Washington, D. C., National Academy of Sciences - National Research Council Publication 1487, 1967.

10. Michaelson, S. M., Woodward, K. T., Odland, L. T. and Howland, J. W. Radiation time-intensity and pathophysiologic correlations in whole and partial-body X-irradiated beagles. In: Dose Rate in Mammalian Radiation Biology, Proceedings of a Symposium co-sponsored by UT-AEC Agricultural Research Laboratory, Brown, D. G., Cragle, R. G. and Noonan, T. R., editors, pp. 7.1 - 7.21. Oak Ridge, Tennessee, United States Atomic Energy Commission, Division of Technical Information, CONF-680410 (TID-4500), 1968.

11. Rubin, P. and Casarett, G. W. Hematopoietic tissues and blood. In: Clinical Radiation Pathology, Vol. II, pp. 778-849. Philadelphia, London and Toronto, W. B. Saunders Company, 1968.

12. Schalm, O. W. Veterinary Hematology, 2nd ed., pp. 46-129. Philadelphia, Pennsylvania, Lea and Febiger, 1965.

13. Silini, G., Elli, R., Siracusa, G. and Kallman, R. F. The radiosensitivity of hemopoietic stem cells after conditioning irradiation. Radiation Res. 31:603-604 (Abstract Dd-9), 1967.

14. West, J. E. Dose rate effects on bone marrow cellularity after simulated solar flare irradiation in beagles. Ph. D. Thesis, Davis, California, University of California [Ann Arbor, Michigan, University Microfilms, Inc., No. 72-3612], 1971.

15. West, J. E., Mitchell, F. A. and Vagher, J. P. Serial rib marrow aspiration technique and myelogram for adult beagles. Bethesda, Maryland, Armed Forces Radiobiology Research Institute Technical Note TN71-1, 1971.

16. Wintrobe, M. M. Clinical Hematology, 6th ed., pp. 295-344. Philadelphia, Pennsylvania, Lea and Febiger, 1967.

UNCLASSIFIED
Security Classification

**DOCUMENT CONTROL DATA - R & D**

*(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)*

| 1. ORIGINATING ACTIVITY (Corporate author) | 2a. REPORT SECURITY CLASSIFICATION |
|---|---|
| Armed Forces Radiobiology Research Institute<br>Defense Nuclear Agency<br>Bethesda, Maryland 20014 | UNCLASSIFIED<br>2b. GROUP<br>N/A |

3. REPORT TITLE

BONE MARROW RESPONSE OF BEAGLES TO FRACTIONATED DOSES OF MIXED GAMMA-NEUTRON RADIATION

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

5. AUTHOR(S) (First name, middle initial, last name)

J. E. West, F. A. Mitchell, S. R. Jones and J. Witz

| 6. REPORT DATE | 7a. TOTAL NO. OF PAGES | 7b. NO. OF REFS |
|---|---|---|
| September 1973 | 20 | 16 |

| 8a. CONTRACT OR GRANT NO. | 9a. ORIGINATOR'S REPORT NUMBER(S) |
|---|---|
| b. PROJECT NO. NWED QAXM | AFRRI SR73-15 |
| c. Task and Subtask C 903 | 9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report) |
| d. Work Unit 02 | |

10. DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited

| 11. SUPPLEMENTARY NOTES | 12. SPONSORING MILITARY ACTIVITY |
|---|---|
| | Director<br>Defense Nuclear Agency<br>Washington, D. C. 20305 |

13. ABSTRACT

Male beagles were bilaterally exposed to mixed gamma-neutron radiation from the AFRRI-TRIGA reactor. The dose rate was 20 rads/minute for all irradiations and midline tissue doses were 215 rads, 225 rads and 240 rads. At each dose approximately one-half of the animals received a single irradiation while the others were given one-fourth the dose each day for 4 consecutive days. The objective of this study was to determine if doses in the median lethal range delivered in four equal fractions at 24-hour intervals were more lethal and more damaging to survival-limiting hematopoietic cell renewal systems than similar, unfractionated doses. Serial rib marrow aspirates and peripheral blood samples were studied for 32 days after irradiation. Single irradiations were the more lethal, first evident at 225 rads and increasing markedly in effectiveness at 240 rads. Radiation-induced changes in bone marrow cellularity were similar after single and fractionated irradiations. Thus, data did not support an enhanced effect on key end points as would have been expected from mitotic cell cycle synchronization and increased marrow cell death from the carefully spaced dose fractions.

DD FORM 1 NOV 65 1473

UNCLASSIFIED
Security Classification